

ABSTRACT

The present invention is directed to methods for detecting or measuring Notch activation by observing or measuring the appearance of Notch on the cell surface or by  
5 observing or measuring Notch cleavage products that are indicative of Notch activation. The present invention is also directed to methods for detecting a molecule that modulates Notch activation by observing or measuring a change in the amount of Notch expressed on the cell surface or a  
10 change in the amount or pattern of Notch cleavage products. The present invention is also directed to a substantially purified activated heterodimeric form of Notch and components thereof and pharmaceutical compositions and kits thereof. The present invention is based, at least in part, on the  
15 discovery that Notch in its active form, *i.e.*, the form that mediates signal transduction and that binds Notch ligands such as Delta, is a heterodimer of an about 180 kDa subunit ( $N^{EC}$ ) and an about 110 kDa subunit ( $N^{TM}$ ), which are tethered together through a reducing agent-sensitive linkage, in  
20 particular, a non-covalent, metal ion-dependent linkage.

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